

REMARKS

This is in response to the Office Action mailed November 15, 2006, having a three-month shortened statutory period for reply set to expire February 15, 2006. Applicants respectfully request the reconsideration and allowance of the above-identified patent application. Please credit any overpayment or, alternatively, charge any fee deficiency to Deposit Account No. 13-2755.

Claims 1-83 are currently pending in the present application. Claims 12-20, 24-29, 31-44, 46-57, 59-72, and 74-83 have been withdrawn from consideration in accordance with an imposed restriction requirement. Claims 1-11, 21-23, 30, 45, 58, and 73 are under examination. Claim 11 has been amended in efforts to advance prosecution on the merits, with support to be found, *inter alia*, at page 10, lines 30-33. No new matter has been added.

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks:

REJECTION UNDER 35 U.S.C. §112, Second Paragraph

Claim 11 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The claim, allegedly, fails to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse.

Claim 11 is rejected for use of the trademark PER.C6™. The use of a trademark, allegedly, renders the claim scope uncertain.

In efforts to advance prosecution on the merits, Applicants have amended claim 11 to speak to Ad5 E1- complementing cell lines, the term of which includes the PER.C6™ cell line. Support can be found, *inter alia*, at page 10, lines 30-33.

Based on the foregoing, Applicants respectfully request the reconsideration, and withdrawal, of the rejection under 35 U.S.C. §112, second paragraph.

REJECTION UNDER 35 U.S.C. §103(a)

Claims 1-11 and 21 are rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,849,561 ("Falck-Pedersen *et al.*"), further in view of Lusky *et al.*, 1998 *J. Virol.* 72:2022-2032 ("Lusky *et al.*"); U.S. Patent No. 7,026,164 ("Li *et al.*"); Basler & Horwitz, 1996 *Virol.* 215:165-177 ("Basler & Horwitz"); and U.S. Patent No. 6,475,480 ("Mehtali *et al.*"). Applicants respectfully traverse.

REJECTION

The claims are rejected over a combination of teachings that, together, are said to render the claimed methods obvious. The references are cited as follows: Falck-Pedersen is cited for teaching the production of replication-defective adenovirus deficient in E1 and E4 in cells providing, *in trans*, gene functions of E1 and E4; said E1 and E4 of the cell line which are of one serotype and said adenovirus (inclusive of E4) of another serotype. Basler & Horwitz is cited for studying Ad35 versus Ad2 mRNA processing. Mehtali *et al.* is cited for teaching the use of a polynucleotide encoding one or more ORF(s) of the E4 region in replication-defective adenoviruses for purposes of improving the expression and/or persistence of a gene of interest. Mehtali *et al.* is, further, cited for teaching insertion of a heterologous E4 region where an E4 region has been deleted. Mehtali is also cited for teaching the provision of E4 ORF *in cis* or *in trans* to an E4-deleted vector. Li *et al.* is cited for teaching PER.C6 cells to reduce unwanted recombination events between the cell line and the vector. Lusky *et al.* is cited for the principle that deletion of E1 is sufficient to impair expression of viral genes. Applicants respectfully traverse.

OBVIOUSNESS UNDER 35 USC §103

The initial burden of presenting a prima facie case of obviousness rests on the Examiner. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Examiner must show: (1) a suggestion or motivation in the prior art to modify or combine the references; (2) a reasonable expectation of success based on the disclosure of the references and (3) disclosure of all of the claim limitations within the prior art. MPEP § 2143. Only after a proper prima facie case of obviousness is established does the burden of rebutting same shift to the Applicants.

SUMMARY

In the present case, Applicants assert that the Office Action fails to establish a prima facie case of obviousness because the combination of references cited in the Office Action does not (1) provide a suggestion or motivation in the prior art to combine the references; (2) disclose sufficient information to allow the skilled artisan to carry out the presently claimed methods with a reasonable expectation of success; or (3) disclose every limitation of the claims at issue.

Accordingly, the combination of teachings fails to teach or suggest a method for growing replication-defective adenovirus in an E1-complementing cell line irrespective of the serotype or make-up of the E1-complementing cell line.

Rather, the cited references reiterate the state of the art at the time of the instant filing – wherein the cell line was factored in or manipulated to allow for the growth of replication-defective adenovirus of a serotype different from the E1 expressed by the complementing cell line. It was not understood or appreciated that E4 within the virus could be manipulated or, in the alternative, supplemented by that of an alternative serotype for purposes of propagating the adenovirus in an existing cell line.

CLAIMED INVENTION

Claim 1 is drawn to a method for enabling the propagation of replication-defective adenovirus in an adenoviral E1-complementing cell line where the adenoviral E1-complementing cell line expresses an E1 gene product(s) which is not of the same serotype as the replication-defective adenovirus. The method involves the insertion of all or a portion of a heterologous adenoviral E4 region comprising a nucleic acid sequence encoding open reading frame 6 (ORF6) into a replication-defective adenovirus; wherein the E4 region or portion thereof is of the same adenovirus serotype as the E1 gene product(s) expressed by the complementing cell line, introducing the replication-defective adenovirus into the adenoviral E1-complementing cell line, allowing the replication-defective adenovirus to propagate in the adenoviral E1-complementing cell line, and rescuing the propagated adenovirus.

Claims 2-11 and 21 depend off of, and further limit, claim 1.

FALCK-PEDERSEN TEACHINGS

Falck-Pedersen teaches the production of replication-defective adenovirus deficient in E1 in a cell line providing *in trans* gene functions of E1 and E4; said E1 and E4 of a different subgroup than the adenovirus being propagated.

Falck-Pedersen does not teach the use of providing a heterologous E4 region *in cis* within the replication-defective adenovirus.

Furthermore, Falck-Pedersen does not speak to or suggest that cell lines providing E1 and E4 of one serotype would be sufficient to complement an adenovirus of a distinct serotype which is deleted in E4. Note that the adenovirus of Falck-Pedersen are deleted in E1 only; *see* Abstract; Brief Summary of the Invention (line 54); Col. 7 (line 66); Col. 8 (lines 20-22; lines 35-37); and Examples.

The teachings of Falck-Pedersen, therefore, do not provide for Applicants' methods which provide for the incorporation of a heterologous E4 *of an alternative serotype* into an adenoviral vector which, in specific embodiments, may take the place of the native E4 region for purposes of enabling the growth in an E1-complementing cell line providing an E1 of alternative serotype to the vector.

Applicants' methods are a significant contribution to the art in that the methods permit, for the first time, the skilled artisan to avoid having to tailor the cell line to each individual vector.

The absence of such a teaching in the literature and the continued recitation of more cumbersome and tedious processes ultimately amounts to a teaching away of the presently claimed methods.

MEHTALI ET AL. TEACHINGS

The deficiencies in the teachings of Falck-Pedersen are, furthermore, not cured by the recitation of Mehtali *et al.*

Mehtali *et al.* is cited for teaching the use of a polynucleotide encoding one or more ORF(s) of the E4 region in replication-defective adenoviruses to improve the expression and/or persistence of a gene of interest. Mehtali *et al.* is particularly cited for teaching the insertion of a heterologous E4 region where an E4 region has been deleted. Mehtali is also cited for the provision of E4 ORF *in cis* or *in trans* to an E4-deleted vector.

Mehtali *et al.* teaches that specific E4 segments, when retained in adenovirus, maintain sufficient expression and/or persistence of a gene of interest contained therein.

The combined teachings of Falck-Pedersen and Mehtali *et al.* can, at most, provide the motivation for cell lines expressing E1 and E4 of one serotype for the complementation of E1-deficient adenovirus of an alternative serotype wherein the adenovirus has, at least, the specified region of the same or similar serotype as the virus, as discussed in Mehtali *et al.* There is no teaching or suggestion in either reference that the E4 region could be swapped out in favor of or, in the alternative, supplemented with one of alternative serotype. Most importantly, there is no teaching or suggestion that such a manipulation could enable the production of said adenovirus in an E1-complementing cell line expressing an E1 of the same serogroup as the E4 in the adenovirus. In fact, the skilled artisan would be uncertain about this given the noted criticality of ORFs 3 and 6 in terms of viral growth; col. 2, lines 9-13.

In fact, Mehtali *et al.* specifically provides that the cell line can be propagated in a complementation cell line, which supplies *in trans* the deleted/mutated viral functions; and even recites E1, E4 cell lines capable of complementing doubly defective vectors. Accordingly, there is clearly no recognition that the vector could be so manipulated so as not to require such a complementing cell line.

Applicants submit, furthermore, that there is not a motivation to combine the teachings. Mehtali *et al.*'s teachings revolve around improving expression and/or persistence of a gene of interest. There is no discussion or suggestion of the use of various E4 regions to enhance E1's complementation of an adenoviral vector deleted of an E1 of alternative serotype.

Accordingly, Applicants submit that the combination of Falck-Pedersen and Mehtali *et al.* fails to provide for the presently claimed methods. The additional references equally fail to render the present invention obvious under 35 U.S.C. §103, as specified below.

SUPPLEMENTAL REFERENCES TEACHINGS

Lusky *et al.* is cited for teaching that deletion of E1 is sufficient to impair expression of viral genes.

Basler & Horwitz are cited for Ad35.

Li *et al.* is cited for production in PER.C6 cells.

Not one of these references suggests or renders obvious the manipulation of adenovirus to specifically express an E4 region of an alternative serotype, said alternative serotype which is representative of the E1 provided by the complementing cell line. Not one of these references even suggests or implies that said manipulation is feasible, and particularly feasible for producing such adenovirus in an E1-complementing cell line not tailored to the vector. If anything, the multitude of references continue to reaffirm the practices established in the art – specifically, that the cell line need be tailored to the vector.

EXPECTATION OF SUCCESS

The combined teachings, as suggested, fail to disclose all the elements of the present invention. Accordingly, one of skill in the pertinent art would not have had a reasonable expectation of success piecing together the various teachings of the cited references to arrive at the methods of the present invention. There was, furthermore, no guidance or direction for the skilled artisan to ultimately derive the presently claimed methods.

The statement that Applicants' claimed methods were obvious and should have worked, having had the benefit of reading Applicants' disclosure, does not afford Applicants a fair examination of the claims. Applicants' disclosed methods were clearly not ascertained in the field. In addition, there were too many variables that could have negatively impacted viral growth, which may very likely explain why it was not attempted or suggested. The E4 region in the present methods is incorporated in a non-native (alternative serotype) environment. Any such manipulation to the viral genome which changes it from the wild-type sequence to a non-native sequence is unpredictable in terms of its effect on viral growth. The non-native E4 must, furthermore, interact with E1 expressed *in trans* by the cell. This is not predictable, as the expression of viral proteins, including the E4 proteins being introduced in the adenovirus, is

regulated as part of the viral life cycle which is, no doubt, very different – both temporally and qualitatively - from expression from the cellular genome. The effect of all these variables on the ultimate growth of the virus and the feasibility of the methods in the various exemplified embodiments is not obvious.

All of these variables, no doubt, explain why methods such as those described and claimed were not suggested nor attempted in the cited literature.

CONCLUSION

Applicants submit, based on the foregoing arguments, that the combination of teachings fails to render the present invention obvious under 35 U.S.C. §103.

To assert otherwise, would inappropriately and unfairly exploit the benefit of hindsight reconstruction. The fact that this method could be successfully practiced for purposes of the present invention was clearly not appreciated in the art. Caution, therefore, need be exercised so as not to import teachings extracted from the present disclosure into the combined teachings of the cited art. "The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention"; MPEP 2141.

Applicants, therefore, respectfully request the review and reconsideration of the present rejection.

REJECTION UNDER 35 U.S.C. §103(a)

Claims 21-23 are rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,849,561 ("Falck-Pedersen *et al.*"), further in view of Lusky *et al.*, 1998 *J. Virol.* 72:2022-2032 ("Lusky *et al.*"); U.S. Patent No. 7,026,164 ("Li *et al.*"); U.S. Patent No. 6,475,480 ("Mehtali *et al.*"); and Megede *et al.*, 2000 *J. Virol.* 74:2628-2635 ("Megede *et al.*"). Applicants respectfully traverse.

REJECTION

The claims are rejected over a combination of teachings that, allegedly, render the claimed methods obvious. The references are cited as follows: Falck-Pedersen is cited for

teaching the production of replication-defective adenovirus deficient in E1 and E4 in cells providing *in trans* gene functions of E1 and E4 that are not of the same subgroup as the adenovirus. Mehtali *et al.* is cited for teaching the use of a polynucleotide encoding one or more ORF(s) of the E4 region in replication-defective adenoviruses for purposes of improving the expression and/or persistence of a gene of interest. Mehtali *et al.* is also cited for teaching insertion of a heterologous E4 region where an E4 region has been deleted. Mehtali is also cited for teaching the provision of E4 ORF *in cis* or *in trans* to an E4-deleted vector. Li *et al.* is cited for teaching PER.C6 cells to reduce unwanted recombination events between the cell line and the vector. Lusky *et al.* is cited for the principle that deletion of E1 is sufficient to impair expression of viral genes. Megede *et al.* is cited for teaching that HIV-1 gag is an important target for host cell-mediated immune control of the virus during infection. Applicants respectfully traverse.

OBVIOUSNESS UNDER 35 USC §103

The initial burden of presenting a prima facie case of obviousness rests on the Examiner. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Examiner must show: (1) a suggestion or motivation in the prior art to modify or combine the references; (2) a reasonable expectation of success based on the disclosure of the references and (3) disclosure of all of the claim limitations within the prior art. MPEP § 2143. Only after a proper prima facie case of obviousness is established does the burden of rebutting same shift to the Applicants.

SUMMARY

For the reasons specified in response to the prior rejection, Applicants assert that the Office Action fails to establish a prima facie case of obviousness because the combination of references cited in the Office Action does not (1) provide a suggestion or motivation in the prior art to combine the references; (2) disclose sufficient information to allow the skilled artisan to carry out the presently claimed methods with a reasonable expectation of success; or (3) disclose every limitation of the claims at issue.

More specifically, the combination of references does not teach or suggest a method for growing replication-defective adenovirus in an E1-complementing cell line irrespective of the serotype or make-up of the E1-complementing cell line.

Rather, the cited references reiterate the understanding within the art at the time of the instant filing – that the cell line need be factored in or manipulated to allow for the growth of replication-defective adenovirus of a serotype different from the E1 expressed by the complementing cell line. It was not understood or appreciated that E4 could be manipulated to or, in the alternative, supplemented by that of an alternative serotype for purposes of propagating the adenovirus in such a cell line.

CLAIMED INVENTION

Claims 21-23 are drawn to a method for enabling the propagation of replication-defective adenovirus in an adenoviral E1-complementing cell line where the adenoviral E1-complementing cell line expresses an E1 gene product(s) which is not of the same serotype as the replication-defective adenovirus. The method involves the insertion of all or a portion of a heterologous adenoviral E4 region comprising a nucleic acid sequence encoding open reading frame 6 (ORF6) into a replication-defective adenovirus; wherein the E4 region or portion thereof is of the same adenovirus serotype as the E1 gene product(s) expressed by the complementing cell line, introducing the replication-defective adenovirus into the adenoviral E1-complementing cell line, allowing the replication-defective adenovirus to propagate in the adenoviral E1-complementing cell line, and rescuing the propagated adenovirus.

Claim 21 further specifies that the virus has a heterologous gene of interest. Claim 22 specifies that the heterologous gene of interest encodes an HIV-1 antigen. Claim 23 specifies that the HIV-1 antigen is Gag, Pol, Nef and/or Env.

REFERENCES CITED

For the reasons specified in the response to the prior rejection, Applicants submit that the combination of teachings fails to suggest or provide a motivation for arriving at the presently claimed methods. The citation of Megede *et al.* does not cure the noted deficiencies. Megede *et al.*'s sole contribution is the supply of HIV-1 Gag as an antigen of interest. The disclosure, thus, fails to teach the methods as disclosed and claimed in the present application for vectors expressing Gag. Megede *et al.*, furthermore, administers nucleic acid encoding HIV-1 Gag with plasmid DNA or recombinant vaccinia virus. Megede *et al.* can not, therefore, be said to contribute to the art in terms of methods related to adenovirus.

CONCLUSION

Applicants submit, based on the foregoing arguments, that the combination of teachings fails to render the present invention obvious under 35 U.S.C. §103.

As stated prior, to assert otherwise, would inappropriately and unfairly exploit the benefit of hindsight reconstruction. The fact that this method could be successfully practiced for purposes of the present invention was clearly not appreciated in the art. Caution, therefore, need be exercised so as not to import teachings extracted from the present disclosure into the combined teachings of the cited art. "The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention"; MPEP 2141.

Applicants, thus, respectfully request the review and reconsideration of the present rejection.

In summary, Applicants maintain all claims are in condition for allowance and earnestly solicit a favorable action on the merits.

Respectfully submitted,

By 

Anna L. Cocuzzo
Reg. No. 42,452
Attorney for Applicant

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1273

Date: February 14, 2007